REMARKS

Claims 1 and 19-21 will be pending upon entry of this Reply. Claims 2-18 have been canceled without prejudice in view of their withdrawal from consideration due to a restriction requirement. Applicants fully reserve all rights to pursue the subject matters of claims 2-18 in a related application.

The title has been amended to recite "Methods for Screening for Selective Anxiolytic Therapeutic Agents" in order to be more descriptive of the claimed subject matter.

Claims 1 and 19-21 have been amended to recite that the candidate molecule selectively or preferentially activates the α2-$GABA_A$ receptor as compared to the α1-$GABA_A$ receptor. Applicants submit that the claims as amended are equivalent in scope since in order for a molecule to activate the receptor, it has to bind the receptor.

No new matter is added by the amendments made herein.

1. Rejections under 35 U.S.C.. § 112, First Paragraph

A. Claims 1 and 19-21 are rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. According to the Examiner, "the specification, while being enabling for a method demonstrating that α2-$GABA_A$ receptor knock-out mice do not show anxiolytic effects when administered benzodiazepine, does not reasonably provide enablement for the claimed screening methods."

Applicants respectfully disagree. Applicants believe that the Examiner has misunderstood the scientific data underlying the invention. Applicants have shown, using a mouse model having a point mutation in the α2-$GABA_A$ receptor, that the α2-$GABA_A$ receptor selectively and exclusively mediates the anxiolytic effects of benzodiazepines, and thus, ligands for this receptor will qualify as anxiolytic agents. Applicants have not used

knock-out mice, as alleged by the Examiner.

Applicants invite the Examiner's attention to Section 6.2 on pages 26-28 of the application, wherein the experimental results obtained by Applicants are discussed. As taught therein, two mutant mouse lines were created using homologous recombination techniques in which one mouse line contained a point mutation in the gene coding for the $\alpha 2$-$GABA_A$ receptor and the other mouse line contained a point mutation in the $\alpha 3$-$GABA_A$ receptor. Each of these mutations abolished binding of diazepam to the respective receptors but the mice were normal in every other way. Thus, in the $\alpha 2$ receptor point mutated mice, the $\alpha 1$, $\alpha 3$ and $\alpha 5$ receptors were wild type and bound to diazepam; and in the $\alpha 3$ receptor point mutated mice, the $\alpha 1$, $\alpha 2$ and $\alpha 5$ receptors were wild type and bound to diazepam.

These mouse lines were then used in a number of well-known and art-accepted experimental models for measuring the sedative and/or anxiolytic activities of compounds, including benzodiazepines, in mice. The data showed that only the $\alpha 2$-$GABA_A$ receptor mediated the anxiolytic activity of diazepam. The mutation in the $\alpha 3$-$GABA_A$ receptor had no effect on the anxiolytic effect of diazepam. Importantly, the sedative effects of diazepam were also not effected by the point mutation in either the $\alpha 2$- or $\alpha 3$-$GABA_A$ receptors, which is consistent with the teaching of Rudolph *et al.*, 1999, Nature 401:796-800 (Reference C08 of record), which discloses that the $\alpha 1$-$GABA_A$ receptor mediates the sedative effects of benzodiazepines but does not affect the anxiolytic activity (in the Rudolph *et al.* experiments, the mouse line contained a point mutation in the $\alpha 1$ receptor abolishing diazepam binding, but the $\alpha 2$, $\alpha 3$ and $\alpha 5$ receptors were wild type and bound to diazepam).

Thus, Applicants have shown that (i) a mutation in the $\alpha 2$-$GABA_A$ receptor abolishes completely the anxiolytic activity of diazepam, but its sedative activity is unaffected; (ii) a mutation in the $\alpha 3$-$GABA_A$ receptor does not have an effect on either of the anxiolytic or the sedative activity of diazepam; and (iii) Rudolph *et al.* showed that a similarly mutated $\alpha 1$-$GABA_A$ receptor abolished the sedative activity of diazepam but did not

effect its anxiolytic activity. These data together clearly show that the $\alpha 2$-$GABA_A$ receptor is the exclusive target for anxiolytic activity and that no other $GABA_A$ receptor is involved, including the $\alpha 3$- and $\alpha 5$-$GABA_A$ receptors.

Further, Applicants invite the Examiner's attention to Section 5 of the specification, which clearly describes and enables methods for screening a selective anxiolytic therapeutic agent that selectively or preferentially binds to the $\alpha 2$-$GABA_A$ receptor as compared to the $\alpha 1$-$GABA_A$ receptor, which agent allows for the treatment of an anxiety-related disorder while minimizing the unwanted side effects of such treatment mediated through the $\alpha 1$-$GABA_A$ receptor. The method comprises contacting a candidate molecule (test agent) with the $\alpha 2$-$GABA_A$ receptor and the $\alpha 1$-$GABA_A$ receptor and determining whether the candidate molecule selectively or preferentially activates the $\alpha 2$-$GABA_A$ receptor as compared to the $\alpha 1$-$GABA_A$ receptor. The specification in Sections 5.1 and 5.2 further describes and enables a number of screening methods which can be used in carrying out the present invention.

In view of the foregoing teachings of the specification, including the experimental evidence demonstrating that the $\alpha 2$-$GABA_A$ receptor is the exclusive mediator of the anxiolytic effects of benzodiazepines, methods for screening for compounds that are selectively anxiolytic by comparing the relative ability of a test compound to activate $\alpha 2$-$GABA_A$ receptors as compared to $\alpha 1$-$GABA_A$ receptors are clearly enabled. Thus, Applicants respectfully request withdrawal of this Section 112, first paragraph, rejection.

B. Claims 1 and 19-21 are rejected under 35 U.S.C. § 112, first paragraph, allegedly as containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. According to the Examiner, Applicants have not identified any compounds which selectively bind the $\alpha 2$-$GABA_A$ receptor to reduce anxiety.

Applicants respectfully disagree with the rejection and note that the claims have been amended to recite a method for screening to identify a selective anxiolytic agent comprising contacting a candidate molecule with the $\alpha 2$-$GABA_A$ receptor and the $\alpha 1$-$GABA_A$ receptor and determining whether the candidate molecule selectively or preferentially activates the $\alpha 2$-$GABA_A$ receptor as compared to the $\alpha 1$-$GABA_A$ receptor, wherein a molecule that selectively or preferentially activates the $\alpha 2$-$GABA_A$ receptor as compared to the $\alpha 1$-$GABA_A$ receptor is a selective anxiolytic agent.

Additionally, the Examiner seems to have misinterpreted the claims. The Examiner's rejection seems to be predicated on the fact that the claims are directed to compounds that are selective anxiolytic compounds. However, this is not the case. The claims are directed to screening methods. As such, Applicants do not understand the Examiner's rejection and request that it be clarified.

In view of the foregoing, the rejections under Section 112, first paragraph, have been overcome and Applicants respectfully request their withdrawal.

2. Rejections under 35 U.S.C. § 112, Second Paragraph

A. Claims 1 and 19-21 are rejected under 35 U.S.C. § 112, second paragraph, allegedly as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. According to the Examiner, the claims are confusing since it is not clear how a compound which simply binds to a receptor would have any effects. In response, Applicants have amended claims 1 and 19-21 to recite that the method comprises determining whether the candidate molecule selectively or preferentially activates the GABA receptor. Applicants submit that this amendment has no effect on the scope of the claims since it is clear that a candidate molecule will have to bind the receptor in order to activate it. In view of the claim amendments, Applicants submit that this rejection has been obviated.

B. Claims 19-21 are rejected under 35 U.S.C. § 112, second paragraph, allegedly as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. According to the Examiner, it is not clear how the applicants have concluded that the $\alpha 5$ receptor has no effect on anxiolytic activity. In response, Applicants invite the Examiner to review the experimental evidence discussed above showing that only the $\alpha 2$-$GABA_A$ receptors mediate any anxiolytic activity. Note that in all the experiments, wild-type $\alpha 5$-$GABA_A$ receptors were present and expressed in the mouse lines. In view of these results, it can be reasonably concluded that the $\alpha 5$-$GABA_A$ receptors have no role in mediating anxiolytic activity.

In view of the foregoing, Applicants respectfully submit that the rejections under Section 112, second paragraph, have been overcome and/or obviated and, thus, request their withdrawal.

3. Rejections under 35 U.S.C. § 102

A. Claims 1 and 19-21 have been rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,444,666 to Ladduwahetty *et al.* (Ladduwahetty). According to the Examiner, Ladduwahetty teaches that compounds which selectively bind the $\alpha 2$-$GABA_A$ and/or $\alpha 3$-$GABA_A$ receptor as compared to the $\alpha 1$-$GABA_A$ will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Further, according to the Examiner, although the "reference is silent to the use of screening methods, the artisan would immediately envision these methods." The Examiner continues in stating that "it is inherent in the identification of the compounds of the patent that screening methods must be employed in order to determine the selectivity of the produced compounds."

Applicants respectfully disagree. In order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565 (Fed. Cir. 1985). "Anticipation under

Section 102 can be found only if a reference shows exactly what is claimed . . ." *Structural Rubber Prod. Co. v. Park Rubber Co.*, 749 F.2d 707 (Fed. Cir. 1984). The presently pending claims are directed to a method for screening to identify a selective anxiolytic agent comprising contacting a candidate molecule with the $\alpha 2$-$GABA_A$ receptor and the $\alpha 1$-$GABA_A$ receptor and determining whether the candidate molecule selectively or preferentially activates the $\alpha 2$-$GABA_A$ receptor as compared to the $\alpha 1$-$GABA_A$ receptor. Ladduwahetty does not teach such a method, nor has such a method been carried out inherently. As disclosed in Ladduwahetty in column 17, lines 1-10, certain compounds were merely tested to determine the K_i value (binding constant) on the $\alpha 2$, $\alpha 3$ and/or $\alpha 5$ receptors. There was no measurement with regard to the $\alpha 1$ receptor, nor was there any comparison between the values obtained for the $\alpha 1$ receptor with those obtained for the $\alpha 2$ receptor. Further, the claims require that the activation of the receptor be measured, not mere binding to the receptor. As determination of activity or determination of relative activity of $\alpha 2$ compared to $\alpha 1$ was not performed, the claimed methods were not performed, either directly or inherently. Thus, Ladduwahetty does not anticipate the claimed invention.

B. Claims 1 and 19-21 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Rudolph *et al.*, 1999, Nature 401:796-800 (Rudolph). According to the Examiner, Rudolph teaches that the anxiolytic compounds likely act via the $\alpha 2$, $\alpha 3$ or $\alpha 5$ receptor but not through the $\alpha 1$ receptor. The Examiner continues in stating that "it is inherent in the identification of the compounds of the patent that screening methods must be employed in order to determine the selectivity of the produced compounds."

Applicants again disagree and note for the same reasons as discussed above for Ladduwahetty, Rudolph does not anticipate the claimed methods of the invention. Rudolph teaches that the $\alpha 1$-$GABA_A$ receptor mediates the sedative effects of benzodiazepines. However, Rudolph does not teach that $\alpha 2$-$GABA_A$ receptors solely mediate the anxiolytic activity of benzodiazepines, and, thus, Rudolph cannot teach methods for

screening for selective agents by determining the relative ability of test compounds to activate the α2 receptor over the α1 receptor. Rudolph does not anticipate the claimed invention since Rudolph does not disclose each and every element of the claimed methods.

In view of the foregoing, Applicants respectfully submit that the Section 102 rejections have been obviated and request their removal.

4. Rejections under 35 U.S.C. § 103(a)

Claims 1 and 19-21 have been rejected under 35 U.S.C. § 103(a), allegedly, as being obvious over Ladduwahetty or Rudolph, which are each discussed above. Applicants respectfully disagree and submit that neither the disclosure of Ladduwahetty or the disclosure of Rudolph, either alone or in combination, render obvious the claimed subject matter, since neither reference teaches that the α2-$GABA_A$ receptor alone mediates the anxiolytic effects of benzodiazepines. Because of that lack of teaching, neither reference provides the required reasonable expectation of success to achieve the claimed methods.

It was known in the art that of the four $GABA_A$ receptor subtypes involved with mediating the effects of benzodiazepines, α1, α2, α3, and α5, the α1 subtype mediated the sedative action of benzodiazepines. This was demonstrated by Rudolph and by McKernan *et al.*, 2000, Nature Neuroscience 3:567-592 (McKernan, Reference C04, of record). As shown originally by Rudolph, when the α1 receptors were rendered insensitive to diazepam by a point mutation, the sedative action was absent while the anxiolytic activity was unaffected. It was therefore stated that one of the remaining receptors would mediate the anxiolytic effect; however, nothing in Rudolph, McKernan or in Ladduwahetty provides any evidence one way or another as to which of the remaining receptors or combinations thereof mediate the anxiolytic activity.

In Ladduwahetty the only relevant requirement for the ligands is their lack of interaction with α1 receptors relative to α2 and/or α3 (see column 2, line 60 and column 3,

lines 1-3 and 16-18). In addition, Ladduwahetty describes that the ligands have good binding affinity for the $\alpha 5$ receptor (column 10, line 5-6) and can also interact with $\alpha 2$ and/or $\alpha 3$ receptors (column 3, lines 36-38). It is clear that Ladduwahetty does not make any distinction between the $\alpha 2$, $\alpha 3$, or $\alpha 5$ receptors with regard to anxiolytic activity. At best, Ladduwahetty merely speculates that one of the remaining receptors is responsible for anxiolytic activity.

With regard to Rudolph, the disclosure of Rudolph provides no evidence as to which receptor mediates the anxiolytic activity of benzodiazepines. Rudolph does disclose that the $\alpha 1$ receptor mediates the sedative activity, but there is no teaching or suggestion as to which of the remaining receptors would mediate the anxiolytic effects of benzodiazepines.

For a rejection under Section 103(a) for obviousness to be upheld, the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Since none of the cited references provide the requisite teaching that the $\alpha 2$ $GABA_A$ receptor is solely responsible for mediating the anxiolytic effects of benzodiazepines, the cited references do not provide the required expectation of success that the claimed methods can be carried out to identify selective anxiolytic agents. The cited references merely speculate what was already widely known, that a receptor other than the $\alpha 1$ receptor would be responsible for mediating anxiolytic activity.

In view of the foregoing, Applicants respectfully submit that the Section 103 rejections have been overcome, and request their withdrawal.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks of the present response be entered and made of record in the file history present application. Applicants submit that the presently pending claims meet all requirements for patentability and respectfully request allowance and action for issuance.

Applicants request that the Examiner call the undersigned at (212) 790-2803 if any questions or issues remain.

Respectfully submitted,

Date: May 20, 2004

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Enclosures